Remarks

The Office Action mailed September 28, 2001 has been received and reviewed. Claims 1, 4 through 14, 16 through 21, 24 through 26, 28 through 32, and 37 through 58 are pending in the application. All pending claims stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. **Claim Objections**

Claims 28-32 were objected to because there was no article "A" in front of the term "Construct." The informalities have been addressed herein, and applicants respectfully request withdrawal of the objections.

2. **Claim Rejections under 35 U.S.C. § 112, second paragraph**

A. Rejection of Claims 2, 25, 37-40, and 42 under 35 U.S.C. § 112, second paragraph

Claims 2, 25, 37, and claims 38-40 and 42 (depending from claim 2) were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for assertedly failing to particularly point out and distinctly claim what the applicants regard as their invention. Specifically, it was thought that claims 2, 25, 37, and claims 38-40 and 42 depending from claim 2, reciting "significantly" were vague because the "specification fails to define the term 'significantly.'" (Office Action, pages 2-3). Applicants respectfully traverse the rejection.

Claims 2 and 25 recite in part the limitation "significantly reduced tissue tropism for liver cells" and claim 37 recites in part the limitation "significantly reducing an adenovirus capsid of a tissue tropism for liver cells." One of skill in the art would be able to understand the scope of the term "significantly" in light of the specification. The specification clearly indicates that the uptake of chimeric adenovirus by the liver is "significantly" reduced by tabulating the uptake of the control adenovirus by the liver compared to the uptake of chimeric adenovirus by the liver. (*See* Application, Example 2, page 37 and Table II, page 47). Since the the specification provides a standard for

measuring the scope of the term "significantly" in the form of a control against the chimeric adenovirus, one of skill in the art would be able to reasonably understand what is claimed by the applicants. *See* M.P.E.P. § 2173.05(b). Applicants respectfully submit that the remaining claims, as indirectly or directly depending from claim 2, are definite. Reconsideration and withdrawal of the rejections are thus requested.

B. Rejection of Claims 19 and 20 under 35 U.S.C. § 112, second paragraph

Claims 19 and 20 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite because "it is unclear as to the metes and bounds of what would be considered 'means.'" (Office Action, page 3). Applicants have amended the claims, and in view of the amendments respectfully traverse the rejection.

Claim 19 recites in part "a cell for producing a gene delivery vehicle having a tissue tropism for smooth muscle cells said cell comprising means for the assembly of gene delivery vectors." The specification describes the structure, materials, and acts required to support the term "means" recited in claim 19 by describing how the vectors are constructed and propagated. (*See, e.g.*, Application, page 34, line 6). The sixth paragraph of 35 U.S.C. § 112 provides for such use of means terminology ("[a]n element in a claim for combination may be expressed as a means ... for performing a specified function without the recital of structure, material or acts, and such claim shall be construed to cover the corresponding structure, materials, or acts described in the specification and equivalents thereof.") Furthermore, applicants have amended claim 19 to clarify the metes and bounds of what is considered means, as amended claim 19 recites in part "said means includes at least one adenovirus nucleic acid."

Since claim 20 depends from definite claim 19 and does not recite the term "means," claim 20 is also definite. Accordingly, applicants request reconsideration and withdrawal of the rejections.

C. Rejection of Claims 20 and 52 under 35 U.S.C. § 112, second paragraph

Claims 20 and 52 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite because the phrases "originate from" and "originating from" "encompass any number of

derivations such that it is unclear what applicants intend to claim." (Office Action, page 3). Applicants have amended the claims and respectfully request that the rejection be withdrawn.

D. Rejection of Claims 24-26, 47, 49, and 58 under 35 U.S.C. § 112, second paragraph

Claims 24-26, 47, 49, and 58 were rejected under 35 U.S.C. § 112, second paragraph, for assertedly being indefinite for using the term "derived." Specifically, the Office indicated that "the term 'derived' encompasses any number of derivations such that it is unclear as to what applicants intend to claim." (Office Action, page 3). Applicants have amended the claims and respectfully request that the rejections be withdrawn in view of the amendments.

E. Rejection of Claims 44-58 under 35 U.S.C. § 112, second paragraph

Claims 44-58 were rejected under 35 U.S.C. § 112, second paragraph, for assertedly being indefinite because "it is unclear as to what extent is considered 'increased' and what is compared to determine whether the tropism is 'increased' or not." (Office Action, page 3). Applicants have amended the claims, and in view of the amendments respectfully traverse the rejections.

Claims 44 and 58 recite the limitation "increased tissue tropism for endothelial cells." The specification clearly indicates that the specified viruses are able to infect endothelial cells at an increased efficiency when compared to other viruses. (*See* Application, pages 38-89). Furthermore, the applicants have graphed the results of the experiments as described on pages 38-39 of the specification to clearly indicate that the specified viruses have an increased tissue tropism for endothelial cells when compared to other viruses. (*See* Application, FIG. 7A). Applicants have amended claims 44 and 58 to include another virus, or capsid, to compare with the claimed virus such that an "increased tissue tropism" is defined. In view of the amendments, applicants respectfully request reconsideration and withdrawal of the rejections.

Since claims 45-57 depend directly or indirectly from claim 44 and do not recite the term "increased," they are also definite. Reconsideration and withdrawal of the rejections are requested.

F. Rejection of Claim 37 under 35 U.S.C. § 112, second paragraph

Claim 37 was rejected under 35 U.S.C. § 112, second paragraph, as assertedly "being incomplete for omitting essential steps." (Office Action, page 3). Specifically, the Office indicated that the omitted steps were "how to use fiber protein of adenovirus 16 in an adenovirus capsid to significantly reduce an adenovirus capsid of a tissue tropism for liver cells and whether the use of said fiber protein would significantly reduce the tissue tropism for liver cells." (Office Action, page 3). Applicants have amended the claim, and in view of the amendment respectfully traverse the rejection.

Method claim 37 uses the term "comprising" to designate the steps of the claim. The term comprising "is synonymous with 'including,' 'containing,' or 'characterized by,' is inclusive or open-ended and does not exclude additional, unrecited elements or method steps." M.P.E.P. § 2111.03. Applicants have also amended claim 37 to recite in part "incorporating a fragment of a fiber protein" and further submit that one of ordinary skill in the art would know how to incorporate a fragment of a fiber protein of adenovirus 16 into an adenovirus capsid. In view thereof, applicants respectfully request reconsideration and withdrawal of the rejection.

3. **Claim Rejections under 35 U.S.C. § 112, first paragraph**

A. Rejection of Claims 1, 2, 4-14, 16-21, 24-26, and 37-58 under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-14, 16-21, 24-26, and 37-58 were rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in a way to convey to one skilled in the art that the applicants had possession of the claimed invention. Specifically, the Office concluded "that the written description requirement is not satisfied for the genus of proteins or the gene delivery vehicle encoding or carrying said proteins as claimed." (Office Action, page 6). Applicants respectfully traverse the rejection.

The applicants have adequately demonstrated possession of the claimed delivery vehicle comprising protein fragments from at least two different viruses. The application, for instance starting on page 33, and FIGS. 1 through 6 describe methods, sequences, and genetic maps that set

forth the claimed invention. The specification further provides an example of the gene delivery vehicle exhibiting a tropism for smooth muscle cells (*See* Application, page 40 and FIG. 8A). The specification also provides an example of a gene delivery vehicle with an increased tropism for endothelial cells (*See* Application, page 38 and FIG. 7A). The specification further shows an example for a gene delivery vehicle with a significantly reduced tissue tropism for liver cells (*See* Application, page 37 and Table II). Therefore, applicants' invention is characterized by a tropism or lack of tropism for specified cells.

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. § 2164.01(b), *quoting In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). Since each of the above referenced examples provide at least one method for making and using the claimed invention, one of skill in the art would be able to practice the claimed invention. Therefore, reconsideration and withdrawal of the rejections are requested.

B. Rejection of Claims 1, 2, 4-14, 16-21, 24-26, 28-32, and 37-58 under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-14, 16-21, 24-26, 28-32, and 37-58 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabling. Specifically, the Office concluded that "based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan at the time of the invention undue experimentation to practice over the full scope of the claimed invention." (Office Action, page 13). Applicants respectfully traverse the rejection.

"If any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. § 2164.01(c). Since at least one use is enabled in the specification as admitted by the Office, "because the specification, while being enabling for adenovirus 16 chimera," and multiple uses are disclosed, the application is enabling for the multiple uses. (Office Action, page 7). Furthermore, regarding the assertion by the Office that the applicants have not provided an

enabling disclosure with respect to uses of the invention for gene therapy *in vivo,* (*See* Office Action, page 11) the applicants have provided a working *in vitro* example in the specification (*See* Application, Example 2, page 37 and Example 3, page 38) that correlates with a disclosed or claimed method of the invention. As stated in the MPEP, "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." M.P.E.P. § 2164.02.

Applicants respectfully submit that the prior art is not unpredictable as characterized by the Office. The Office cited Rudinger (published in 1976) and Kaye et al. (published in 1990) for supporting the assertion that it is unclear whether an altered tropism-determining protein or chimeric protein would maintain tropism for a specific cell type. (*See* Office Action, page 10-11). However, the cited references describe the effects of mutations in a protein sequence and the effect that the mutation has on the binding of the protein to a target. The cited references do not disclose the differences between *in vitro* and *in vivo* uptake of a chimeric virus by cells. In view of the foregoing analysis, applicants respectfully request reconsideration and withdrawal of the rejections.

C. Rejection of Claims 28-32 under 35 U.S.C. § 112, first paragraph

Claims 28-32 were rejected under 35 U.S.C. § 112, first paragraph, for assertedly containing subject matter that was not described in the specification in a manner to convey to one skilled in the art that the inventors has possession of the claimed invention. Applicants respectfully traverse the rejection. The Office indicated that "the rejection may be obviated by appropriate deposit of the nucleic acid construct claimed." (Office Action, page 13).

Applicants have deposited the constructs of claims 28-32 with the European Collection of Cell Cultures (ECACC). Declaration under 37 C.F.R. §§ 1.801-1.809 and certificates for the claimed constructs from the ECACC indicating that the constructs have been deposited in accordance with the Budapest Treaty and the requirements of the Office Action are enclosed. Withdrawal of the rejections is thus requested.

4. **Claim Rejections under 35 U.S.C. § 102**

Claims 1, 4, 11, 14, 16, 17, 19, and 21 were rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Wickham et al. Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 1 has been amended to recite in part "a tissue tropism determining fragment of a subgroup B adenovirus fiber protein, wherein the tissue tropism determining fragment exhibits at least a tissue tropism for smooth muscle cells." Wickham et al. does not anticipate amended claim 1 because Wickham et al. does not teach using a fragment from a subgroup B adenovirus, but rather Wickham et al. teaches modifying the fiber protein. *See* Wickham et al., pages 8222. Since claims 4 and 11 depend from novel independent claim 1, they are also not anticipated by Wickham et al. Applicants request the anticipation rejection of claim 1 be withdrawn since the cited reference does not disclose each and every element of the amended claim.

With respect to claim 14, Wickham et al. does not anticipate the present claim because the cited reference does not disclose modifying said adenoviral nucleic acid "such that the capacity of said adenoviral nucleic acid to replicate in a target cell has been reduced or disabled." Since Wickham et al. does not teach each and every element set forth in claim 14, applicants request that the claim is not anticipated by the cited reference.

Claim 16 is not anticipated because Wickham et al. does not disclose a gene delivery vehicle comprising a minimal adenovirus vector or an AD/AAV chimeric vector. Applicants request the anticipation rejection of claim 16 be withdrawn since the cited reference does not disclose each and every element of the claim.

Since claim 17 depends on novel independent claim 1, it is not anticipated by Wickham et al. Applicants respectfully request that the rejection be withdrawn.

With respect to claim 19, Wickham et al. does not disclose "a tissue tropism determining fragment of a subgroup B adenoviral fiber protein" as claimed by the applicants. Wickham et al. discloses chimeric adenovirus derived from the E4-minus vector, wherein an RGD integrin-binding sequence or a string of seven lysines is added to the chimeric vector. *See,* Wickham et al., pages 8222-8223. As Wickham et al. fails to teach every limitation of claim 19, applicants submit that the claim is not anticipated by the cited reference.

Claim 21 recites a pharmaceutical composition comprising a gene delivery vehicle together with a suitable vehicle. Wickham et al. does not teach the suitable vehicle. Since the cited reference does not teach each and every element of claim 21, applicants request that the anticipation rejection be withdrawn with respect to claim 21.

5. **Claim Rejections under 35 U.S.C. § 103**

Claims 1, 4-14, 17-19, 24, 26, and 43 were rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Wickham et al. in view of Stevenson et al. and Woo et al. Applicants respectfully traverse the rejection.

M.P.E.P. § 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). (Emphasis added).

A *prima facie* case of obviousness has not been established. The Office asserts that it would have been obvious to substitute DNA encoding the modified fiber protein in Wickham et al. with the chimeric fiber cDNA derived from two adenoviruses (subgroups B and C) taught in Stevenson et al. (*See* Office Action, page 19). However, because Wickham does not teach or suggest using capsid fragments from two different adenoviruses and Stevenson does not teach or suggest a

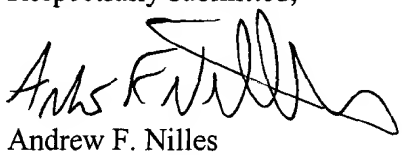
chimeric adenovirus with a tropism for smooth muscle cells, the cited references do not suggest or motivate combining the cited references as suggested by the Office.

The Office also asserts that it would have been obvious to deliver nucleic acid to smooth muscle cells because of the collective teachings of Wickham and Stevenson and the teaching of Woo in treating solid tumors with a recombinant adenoviral vector expressing the HSV-tk gene. (*See*, Office Action, page 20). However, because Woo does not teach or suggest a recombinant adenoviral vector with a tropism for smooth muscle cells and in view of the above analysis with regard to Wickham and Stevenson, a *prima facie* case of obviousness has not been established. Therefore, applicants respectfully request reconsideration and withdrawal of the obviousness rejections.

Conclusion

In view of the amendments and remarks, applicants respectfully submit that the amended claims define patentable subject matter. If any questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Date: February 28, 2002

Enclosures: Marked up Version of Specification Showing Changes Made
Marked up Version of Claims Showing Changes Made
Declaration under 37 C.F.R. §§ 1.801-1.809
Certificates of Deposit from the ECACC

Marked Up Version of Specification

Figure 3: Schematic drawing of construct pBr/Ad.BamRΔfib (ECACC deposit number 01121708).

In another aspect of the invention is provided construct pBr/Ad.BamRΔfib (ECACC deposit number 01121708, deposited on December 12, 2001 with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty, comprising adenovirus 5 sequences 21562-31094 and 32794-35938.

In another aspect of the invention is provided construct pBr/AdBamRfib16 (ECACC deposit number 01121710, deposited on December 12, 2001 with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty, comprising adenovirus 5 sequences 21562-31094 and 32794-3598, further comprising an adenovirus 16 gene encoding fiber protein.

In yet another aspect of the invention is provided construct pBr/AdBamR.pac/fib16 (ECACC deposit number 01121709, deposited on December 12, 2001 with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty, comprising adenovirus 5 sequences 21562-31094 and 32794-35938, further comprising an adenovirus 16 gene encoding fiber protein, and further comprising a unique PacI-site in the proximity of the adenovirus 5 right terminal repeat, in the non-adenovirus sequence backbone of said construct.

In another aspect of the invention is provided construct pWE/Ad.AflIIrITRfib16 (ECACC deposit number 01121711, deposited on December 12, 2001 with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty comprising Ad5 sequence 3534-31094 and 32794-35938, further comprising an adenovirus 16 gene encoding fiber protein.

In another aspect of the invention is provided construct pWE/Ad.AflIIrITRDE2Afib16 (ECACC deposit number 01121712, deposited on December 12, 2001 with the Centre for Applied Microbiology and Research Authority (European Collection of Animal Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty comprising Ad5 sequences 3534-22443 and 24033-31094 and 32794-35938, further comprising an adenovirus 16 gene encoding fiber protein.

All amplified fiber DNAs as well as the vector (pBr/Ad.BamRΔFib) (ECACC deposit number 01121708) were digested with NdeI and NsiI. The digested DNAs were subsequently run on a agarose gel after which the fragments were isolated from the gel and purified using the Geneclean kit (Bio101 Inc). The PCR fragments were then cloned into the NdeI and NsiI sites of pBr/AdBamRΔFib (ECACC deposit number 01121708), thus generating pBr/AdBamRFibXX (where XX stands for the serotype number of which the fiber DNA was isolated). The inserts generated by PCR were sequenced to confirm correct amplification. The obtained sequences of the different fiber genes are shown in Figure 4.

To enable efficient generation of chimaeric viruses an AvrII fragment from the pBr/AdBamRFib16 (ECACC deposit number 01121710), pBr/AdBamRFib28, pBr/AdBamRFib40-L constructs was subcloned into the vector pBr/Ad.Bam-rITR.pac#8 (ECACC deposit #P97082121) replacing the corresponding sequences in this vector. pBr/Ad.Bam-rITR.pac#8 has the same adenoviral insert as pBr/Ad.Bam-rITR but has a PacI site

near the rITR that enables the ITR to be separated from the vector sequences. The constuct pWE/Ad.AflII-Eco was generated as follows. PWE.pac was digested with ClaI and the 5 prime protruding ends were filled in with Klenow enzyme. The DNA was then digested with PacI and isolate from agarose gel. PWE/AflIIrITR was digested with EcoRI and after treatment with Klenow enzyme digested with PacI. The large 24 kb fragment containing the adenoviral sequences was isolated from agarose gel and ligated to the ClaI digested and blundted pWE.Pac vector. Use was made of the ligation express kit from Clontech. After transformation of XL10-gold cells from Stratagene, clones were identified that contained the expected construct. PWE/Ad.AlfII-Eco contains Ad5 sequences from basepairs 3534-27336. Three constructs, pClipsal-Luc (Figure 5) digested with SalI, pWE/Ad.AflII-Eco digested with PacI and EcoRI and pBr/AdBamR.pac/fibXX digested with BamHI and PacI were transfected into adenovirus producer cells (PER.C6, Fallaux *et al*, 1998). Figure 6 schematically depicts the method and fragments used to generate the chimaeric viruses. Only pBr/Ad.BamRfib12 was used without subcloning in the PacI containing vector and therefor was not liberated from vector sequences using PacI but was digested with ClaI which leaves approximately 160 bp of vector sequences attached to the right ITR. Furthermore, the pBr/Ad.BamRfib 12 and pBr/Ad.BamRfib 28 contain an internal BamHI site in the fiber sequences and were therefor digested with SalI which cuts in the vector sequences flanking the BamHI site. For transfection, 2 μg of pCLIPsal-Luc, and 4 μg of both pWE/Ad.AflII-Eco and pBr/AdBamR.pac/fibXX were diluted in serum free DMEM to 100 μl total volume. To this DNA suspension 100 μl 2.5x diluted lipofectamine (Gibco) in serum-free medium was added. After 30 minutes at room temperature the DNA-lipofectamine complex solution was added to 2.5 ml of serum-free DMEM which was subsequently added to a T25 cm^2 tissue culture flask. This flask contained PER.C6 cells that were seeded 24-hours prior to transfection at a density of $1x10^6$ cells/flask. Two hours later, the DNA-lipofectamine complex containing medium was diluted once by the addition of 2.5 ml DMEM supplemented with 20% fetal calf serum. Agains 24 hours later the medium was replaced by fresh DMEM supplemented with 10% fetal calf serum. Cells were cultured for 6-8 days, subsequently harvested, and freeze/thawed 3 times. Cellular debris was removed by centrifugation for 5

minutes at 3000/rpm room temperature. Of the supernatant (12.5 ml) 3-5 ml was used to infect again PER.C6 cells (T80 cm^2 tissue culture flasks). This re-infection results in full cytopathogenic effect (CPE) after 5-6 days after which the adenovirus is harvested as described above.

Marked Up Version of Claims

1. (Thrice amended) A gene delivery vehicle comprising [at least a tissue tropism for smooth muscle cells] a tissue tropism determining fragment of a subgroup B adenovirus fiber protein, wherein the tissue tropism determining fragment exhibits at least a tissue tropism for smooth muscle cells.

4. (Amended) The gene delivery vehicle of claim 1 wherein said tissue tropism determining fragment is [being] provided by a virus capsid.

19. (Thrice amended) A cell for producing a gene delivery [vector] vehicle having a tissue tropism for smooth muscle cells said cell comprising means for the assembly of gene delivery vectors wherein said means includes at [means] least one adenovirus nucleic acid for the production of an adenoviral fiber protein, wherein said adenoviral fiber protein comprises at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein.

20. (Thrice amended) The cell of claim 19, wherein said cell is [or originates from a] of PER.C6 [cell] (ECACC deposit number 96022940) origin.

24. (Thrice amended) An adenovirus capsid having a tissue tropism for smooth muscle cells wherein said capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is [derived from a] of subgroup B adenovirus origin.

25. (Thrice amended) An adenovirus capsid with a significantly reduced tissue tropism for liver cells wherein said adenovirus capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is [derived from a] of subgroup B adenovirus origin.

26. (Thrice amended) A method of delivering nucleic acid to smooth muscle cells, said method comprising:
administering to said smooth muscle cells a gene delivery vehicle comprising an adenovirus capsid comprising proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is [derived from a] of subgroup B adenovirus origin.

28. (Amended) A c[C]onstruct [pBr/Ad.BamRΔFib, comprising adenovirus 5 sequences 21562-31094 and 32794-35938] deposited with the ECACC under deposit number 01121708 on December 12, 2001.

29. (Amended) A c[C]onstruct [pBr/AdBamRfib16, comprising adenovirus 5 sequences 21562-31094 and 32794-35938, and further comprising an adenovirus 16 gene encoding fiber protein] deposited with the ECACC under deposit number 01121710 on December 12, 2001.

30. (Amended) A c[C]onstruct [pBr/AdBamR.pac/fib15, comprising adenovirus 5 sequences 21562-31094 and 32794-35938, an adenovirus 16 gene encoding fiber protein, and a PacI-site in the proximity of the adenovirus 5 right terminal repeat, in the non-adenovirus sequence backbone of said construct] deposited with the ECACC under deposit number 01121709 on December 12, 2001.

31. (Amended) A c[C]onstruct [pWE/Ad.AflIIrITRfib16, comprising adenovirus 5 sequences 3534-31094 and 32794-35938 and an adenovirus 16 gene encoding fiber protein] deposited with the ECACC under deposit number 01121711 on December 12, 2001.

32. (Amended) A c[C]onstruct [pWE/Ad.AflIIrITRDE2Afib16, comprising adenovirus 5 sequences 3534-22443, 24033-31094 and 32794-35938, and further comprising an adenovirus 16 gene encoding fiber protein] deposited with the ECACC under deposit number 0112712 on December 12, 2001.

37. (Thrice amended) A method of [significantly] reducing an adenovirus capsid of a tissue tropism for liver cells, said method comprising [using] incorporating a fragment of a fiber protein of adenovirus 16 in an adenovirus capsid therefor.

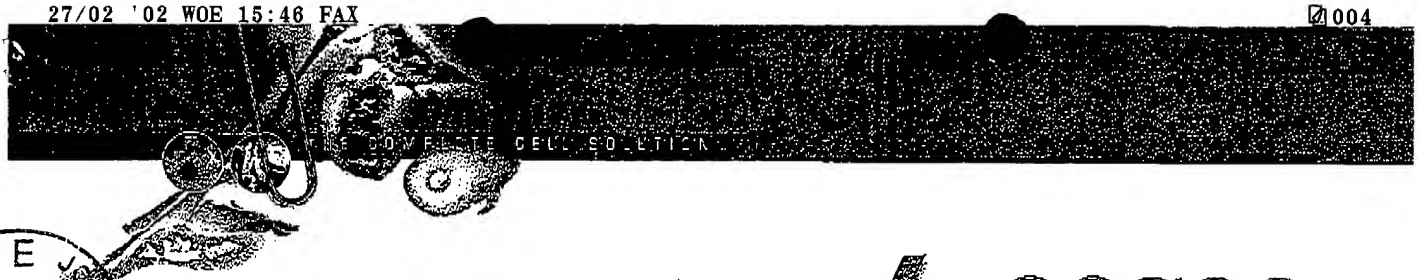
44. (Amended) A gene delivery vehicle comprising increased tissue tropism for endothelial cells when compared to other gene delivery vehicles, wherein said tissue tropism is being provided by a virus capsid and wherein said virus capsid comprises protein fragments from at least two different viruses.

47. (Amended) The gene delivery vehicle of claim 44 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein [derived from a] of subgroup B adenovirus origin.

49. (Amended) The gene delivery vehicle of claim 44 wherein said protein fragments are not from an adenovirus of subgroup B and are [derived from an] of adenovirus of subgroup C origin.

52. (Amended) The gene delivery vehicle of claim 51 wherein said adenoviral nucleic acid comprises sequences [originating] from at least two different adenoviruses.

58. (Amended) An adenovirus capsid having an increased tissue tropism for endothelial cells when compared to other adenovirus capsids, wherein said capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is [derived from a] of subgroup B adenovirus origin.



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This document certifies that

DNA pBr/Ad.BamRdeltaFib.pac

Deposit Reference 01121708

has been accepted as a patent deposit, in accordance with The Budapest Treaty of 1977, with the European Collection of Cell Cultures on 17 December 2001

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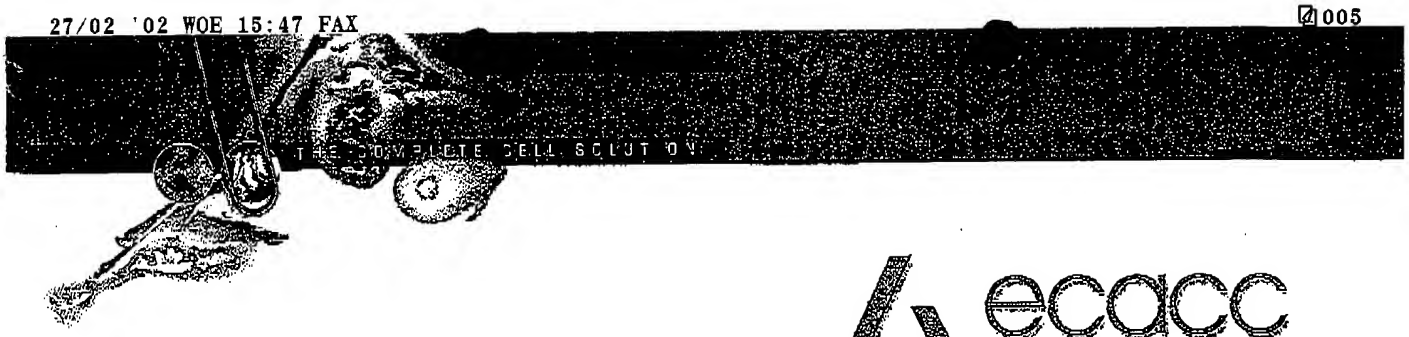

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This document certifies that

DNA pBr/Ad.BamRFib16.pac

Deposit Reference 01121709

has been accepted as a patent deposit, in accordance with The Budapest Treaty of 1977, with the European Collection of Cell Cultures on 17 December 2001

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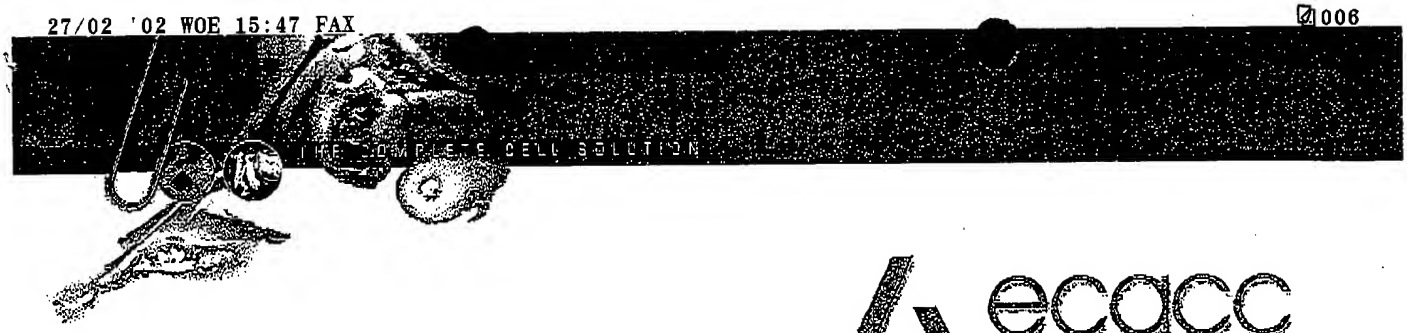

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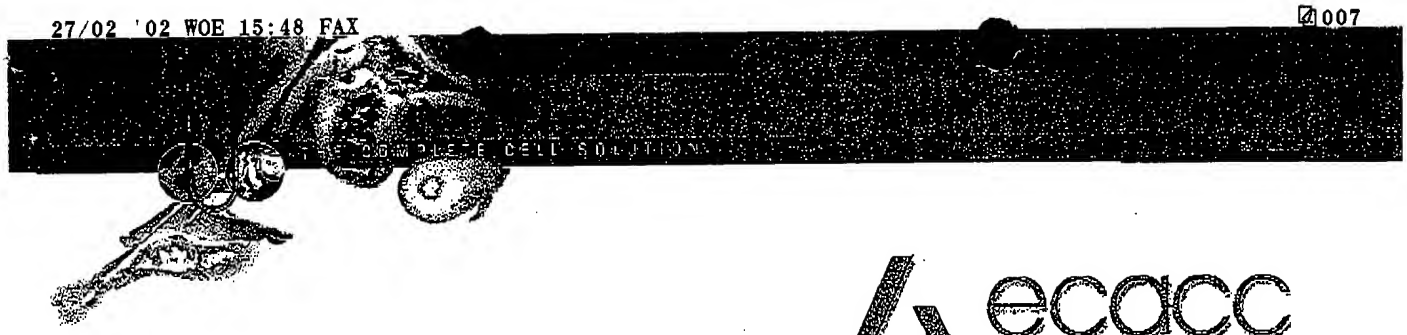

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